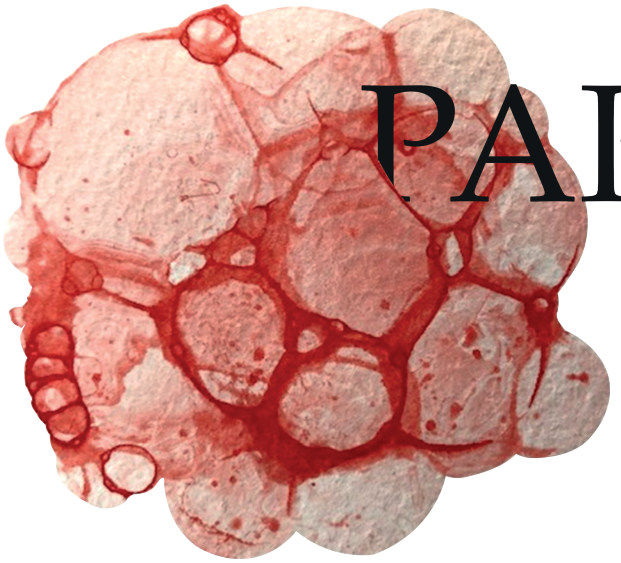

PART III

Preservation of the Brain;

Two Etiologic Factors and the Relation with

Neurodevelopmental Outcome in Preterm Infants

after Necrotizing Enterocolitis

CHAPTER 6

Preterm Infants Undergoing Laparotomy for Necrotizing Enterocolitis or Spontaneous Intestinal Perforation Display Evidence of Impaired Cerebrovascular Autoregulation

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ABSTRACT

Background: Preterm infants requiring surgery are at risk of impaired neurocognitive development caused, possibly, by cerebral ischemia associated with impaired cerebrovascular autoregulation (CAR). We evaluated CAR before, during, and after laparotomy.

Study design: This was a hypothesis generating prospective observational cohort study.

Subjects: We included preterm infants requiring surgery for NEC or spontaneous intestinal perforation (SIP). Before, during, and after surgery we measured cerebral oxygen saturation using NIRS and calculated cerebral fractional tissue oxygen extraction (cFTOE).

Outcome measures: Impaired CAR was defined if correlation coefficients (rho) between mean cFTOE and mean arterial blood pressure values were ≤ -0.30 with $P < .05$. We used logistic regression analyses to determine factors associated with impaired CAR.

Results: Nineteen infants with median (IQR) GA 27.6 weeks (26.6-31.0), birth weight 1090 g (924-1430), and postnatal age 9 days (7-12) were included. CAR was impaired more often during surgery than before (12 versus 3, $P = .02$) or after (12 versus 0, $P < .01$). A higher PCO_2 level was associated with impaired CAR during surgery (OR 3.04, 95% CI, 1.11-8.12 for every 1 kPa increase).

Conclusions: More than half of preterm infants with NEC or SIP displayed evidence of impaired CAR during laparotomy. Further research should focus on mechanisms contributing to impaired CAR in preterm infants during surgery.

INTRODUCTION

Preterm infants who undergo major surgery are at a greater risk of impaired neurodevelopmental outcomes than their peers.[1-4] The most common surgical conditions requiring laparotomy in preterm infants are NEC and spontaneous intestinal perforation (SIP). NEC is a potentially life-threatening inflammatory disease of the intestines. It affects mainly preterm infants, of whom approximately 20% to 40% require surgery.[5] SIP is less common than NEC and always requires surgical intervention.[1]

Several theories have been proposed to explain the pathogenesis of subsequent neurodevelopmental impairment in preterm infants who had undergone major surgery. One possibility is that impaired cerebrovascular autoregulation (CAR) is associated with harmful fluctuations in cerebral perfusion, because in the absence of CAR, cerebral blood flow will passively vary with blood pressure.[6-10] In this case, both hypotension and hypertension may cause neuronal injury. In case of the former there is a risk of cerebral ischemia, while in case of the latter there is a risk of cerebral hemorrhage.[10-14]

Previously, CAR has been assessed non-invasively with NIRS. It is assessed by analyzing the relationship between cerebral oxygen saturation (r_cSO_2), as an indirect measure of cerebral perfusion, and mean arterial blood pressure (MABP), as a surrogate for cerebral perfusion pressure.[14] Regional tissue oxygen saturation (rSO_2), measured by NIRS, is commonly used to assess end-organ perfusion. While decreases in rSO2 might most commonly be caused by decreased perfusion, rSO2 can decline for reasons, such as increases in oxygen demand and consumption.[15,16] The fractional tissue oxygen extraction (FTOE) can be calculated from the rSO_2 and arterial oxygen saturation (SpO_2) values. FTOE, which reflects the balance between oxygen supply and consumption, is less dependent on SpO_2 variations and therefore perhaps a better marker for perfusion,[17] assuming a stable cerebral metabolic rate. CAR is considered to be impaired when cerebral perfusion changes are parallel to changes in MABP.[10,18] On the basis of this principle the adequacy of CAR can be estimated by measuring the correlation between cerebral FTOE (cFTOE) and MABP values. A negative correlation suggests impaired CAR,[10,19,20] where the correlation coefficient might be indicative of the level of impaired CAR. A coefficient of correlation between cerebral tissue oxygen saturation and MABP of > 0.3, was thought to be suggestive of impaired CAR;[21] the threshold coefficient of correlation between FTOE and MBAP should be reversed to < -0.3. Clinical and biochemical factors, such as GA, PCO_2, and the use of anesthetics, may influence autoregulatory capabilities.[8-10,18,22-24]

In order to determine whether surgery and/or anesthesia increase the risk of impaired CAR in preterm infants with NEC or SIP, we evaluated CAR before, during, and after laparotomy. Secondly, we aimed to determine which clinical and biochemical variables were associated with impaired CAR during surgery. We hypothesized that preterm infants have an increased rate of impaired CAR during surgery in comparison to the rates of impaired CAR before and after surgery.

METHODS

Study design

We performed a prospective observational study. All preterm infants with suspected NEC (Bell's classification Stage ≥ 2) or SIP, who required laparotomy between September 2010 and November 2015 and who were admitted to our NICU, were eligible for inclusion. Indications for laparotomy were radiographic signs of free abdominal air or clinical deterioration in conservatively treated NEC infants. The definitive diagnosis, either NEC or SIP, was based on surgical as well as pathological findings. The study was approved by the local ethical review board.

Data collection on cerebral perfusion and MABP measurements

We used an INVOS 5100C near-infrared spectrometer in combination with neonatal SomaSensors (Medtronic, Dublin, Ireland) to measure r_cSO_2. To keep the sensor in place and to protect the vulnerable skin of the preterm infants we placed Mepitel® (Mölnlycke, Sweden) below each sensor. Previous reports stated that Mepitel does not adversely affect INVOS integrity or validity.[25] We placed the sensor on the left or right frontoparietal side of the head and measured r_cSO_2 continuously every 6 seconds. Simultaneously, we measured transcutaneous SpO_2 using Nellcor (Medtronic), every 5 seconds. The cFTOE value was calculated as follows: cFTOE = $(SpO_2\text{-}rSO_2)/SpO_2$ for every 30 seconds that both parameters (r_cSO_2 and SpO_2) were present at the exact same time.

We aimed to collect MABP values every 5 seconds from those infants who had an indwelling arterial catheter, although we managed to maintain MABP data in several patients once every minute due to software limitations. The infants who did not have an indwelling arterial catheter could participate if they had noninvasive blood pressure measurements at a frequency of at least once every five minutes. We collected MABP and r_cSO_2 values simultaneously from a minimum of 30 minutes up to eight hours before surgery, during surgery, and up to eight hours after surgery. We defined the period 'during surgery' as the period from the start of anesthetic administration until the moment that the abdomen was closed. To determine whether an infant had impaired CAR we used the Spearman rank correlation test to calculate the correlation coefficients between the MABP and cFTOE values using all the data from the period of maximal eight hours preoperatively, the period during surgery, and for the period of maximal eight hours postoperatively. Next, impaired CAR was defined as rho ≤ -0.30 and the statistical significance as $P < .05$. For the purpose of this study, infants that did not fulfil these criteria (all correlation coefficients > -0.3) were considered as having no evidence for impaired CAR, from here onward referred to as supposedly adequate CAR. Given the relatively low sample rate of simultaneously collected and stored data (synchronized data of FTOE and MABP every 1-5 minutes), we were not able to perform sophisticated dynamic CAR measurements.

Demographic and clinical variables

Prospectively, we recorded characteristics of the infants including GA, birth weight (BW), gender, Apgar scores at 5 minutes, hemodynamically significant PDA –defined as a PDA that needed treatment according to the attending neonatologist and cardiologist on both clinical and echocardiographic grounds-, postnatal day of diagnosis, either NEC or SIP, postnatal day of surgery, and mortality. Furthermore, we analyzed the last cranial ultrasound before surgery and the first cranial ultrasound after surgery to identify any new cerebral pathology, such as transient periventricular echodensities, germinal matrix hemorrhages, intraventricular hemorrhages, or periventricular leukomalacia. Additionally, we collected data on respiratory support, PCO_2 values collected from blood gases (obtained if clinically indicated) of which we used the last before and the first after surgery. During surgery we averaged the two or three PCO_2 values collected. Furthermore, we collected data on Hb values, lactate values, C-reactive protein, platelet concentrations, volumes of red blood cell transfusions, and need for (saline) volume expansion or inotropes for circulatory support.

Surgical procedure and anesthesia

All included infants underwent an exploratory laparotomy, in supine position, via a transverse upper abdominal incision just above the umbilicus, according to a standardized surgical protocol. We collected data on the time of incision, of opening the abdomen, of resection, of forming a stoma or performing primary anastomosis, and on the time of closing the abdomen. Furthermore, we recorded any medication and fluid therapy that was administered during surgery. Anesthesia was performed by the pediatric anesthesiologist in charge. For the induction and maintenance of anesthesia we used sevoflurane. Analgesia was achieved with fentanyl and muscle relaxation with rocuronium. Postoperative analgesia in the NICU consisted of acetaminophen and morphine. PCO_2 was measured for clinical reasons as ordered by the attending pediatric anesthesiologist. For this study we chose not to use the data on end tidal CO_2 measurements.

Data and statistical analysis

For the statistical analyses we used SPSS 23.0 (IBM Corp., Armonk, NY, USA). To describe the patient characteristics we used median (IQR) values. To evaluate differences between infants with supposedly adequate CAR and infants with impaired CAR we used the Mann-Whitney test or the chi-square test.

We used the McNemar test to compare the presence or absence of CAR (categorized as adequate or impaired) before and during surgery, as well as during surgery and afterwards. Comparisons were made using the Mann-Whitney test or the Friedman test, followed by Wilcoxon signed rank test if statistically significant, whichever was appropriate given the number of measurements and distribution of the data.

Previous research demonstrated that GA, BW, the PCO_2, the concentration of hemoglobin, red blood cell transfusions, and perhaps the use of inotropes or a vasodilatory drug such as sevoflurane, influence r_cSO_2 values[15,24,26] and possibly autoregulatory capabilities.[8,9,17,22-24] Therefore, we wanted to explore the association between these variables and CAR, using univariate logistic regression analyses. We were aware however, that the sample size hampered us from exploring all potential confounders. We converted BW into *z* scores for GA using the Kloosterman curve.[27] Next, we entered the variables with a *P* of < .1 into a multiple logistic regression model using a forward stepwise method to evaluate which variable enters the model with the strongest association and which variables, additionally, contribute to the model. Statistical significance was defined as $P < .05$.

RESULTS

Patient characteristics

We identified 57 eligible infants (Figure 1). For logistic reasons we were only able to perform the NIRS measurements during 27 laparotomies. Out of these 27 infants, MABP measurements were taken from 19 infants at least once every five minutes during surgery as well as before and/or after surgery. These 19 infants were included in the present study. Table 1 contains a complete overview of the patient characteristics. Of the 19 infants, 14 (74%) were diagnosed with NEC and five (26%) with SIP. As shown in the supplemental Table S1, we did not find any statistically significant differences between the characteristics and physiological parameters of NEC and SIP infants, except for preoperative PCO_2 (NEC, 6.5 kPa versus SIP, 5.4 kPa, $P = .03$), the number of infants who received sedatives before surgery (NEC, 9 infants versus SIP, none, $P = .03$), and postoperative hemoglobin values (NEC, 7.6 mmol/L versus. SIP, 9.0 mmol/L, $P = .045$).

We did not find differences in patient characteristics between the 19 included and the 30 non-included infants. The GA (median, IQR) of the non-included infants was 26.9 weeks (26.0-28.9, $P = .11$); BW, 960 g (745-1244, $P = .19$); postnatal age at surgery, 11 days (7-23, $P = .44$); type of diagnosis, SIP 29% and NEC 71% ($P = .84$), and survival rate, 53% survived and 47% died ($P = .45$).

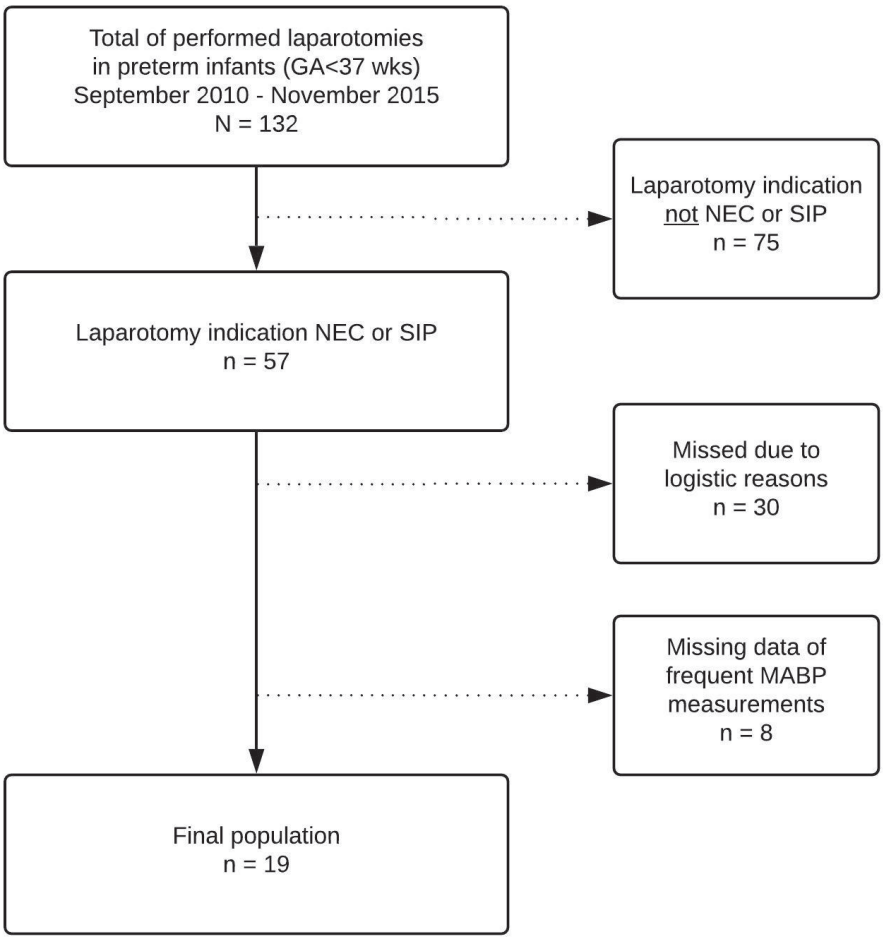

Figure 1. Flow diagram illustrating the inclusion procedure of participants

Table 1. Clinical and biochemical characteristics

	Study group N = 19	CAR+ during surgery n = 7	CAR- during surgery n = 12	P value CAR+ vs. CAR-
Gestational age (wks)	27+4 (26+4-31+0)	29+5 (28+6-34+2)	26+6 (26+2-27+6)	.02*
Birth weight (g)	1090 (924-1430)	1250 (1100-1525)	983 (811-1173)	.06
Male/Female	14/5 (74%/26%)	6/1 (86%/14%)	8/4 (67%/33%)	.60
One of a twin	8 (42%)	5 (71%)	3 (25%)	.07
Apgar score at 5 minutes	7 (6-8)	8 (7-9)	6 (6-8)	.07
Time of clinical symptoms (postnatal day)	7 (5-9)	7 (6-31)	7 (4-8)	.38
Time of surgery (postnatal day)	9 (7-12)	9 (7-31)	10 (4-12)	.71
Diagnosis NEC/SIP	14/5 (74%/26%)	6/1 (86%/14%)	8/4 (67%/33%)	.60
Mortality	7 (37%)			
- From operation indication		1 (14%)	6 (50%)	.17
- From other complications	5 (26%)	1 (14%)	4 (33%)	-
of prematurity	2 (11%)	-	2 (17%)	-
Mean arterial blood pressure (mm Hg)				
- Preoperative	35 (28-38)	39 (35-50)	33 (27-38)	.10
- During surgery	32 (30-36)	33 (31-38)	31 (29-36)	.20
- Postoperative	35 (32-41)	41 (35-42)	35 (30-37)	.09
Saline volume expansion				
- Preoperative	10 (53%)	4 (57%)	6 (50%)	.84
- During surgery	17 (90%)	5 (71%)	12 (100%)	.34
- Postoperative	8 (42%)	4 (57%)	4 (33%)	.48
Inotropes				
- Preoperative	8 (42%)	3 (43%)	5 (42%)	.97
- During surgery	11 (58%)	4 (57%)	7 (58%)	.97
- Postoperative	11 (58%)	4 (57%)	7 (58%)	.86
Sedatives				
- Preoperative	9 (47%)	4 (57%)	5 (42%)	.65
- Postoperative	19 (100%)	7 (100%)	12 (100%)	-
Carbon dioxide (kPa)				
- Preoperative	6.0 (5.4-8.1)	5.8 (5.4-8.1)	6.2 (5.5-8.8)	.62
- During surgery	5.3 (3.7-6.1)	3.7 (2.9-4.7)	6.0 (4.9-6.5)	.01*
- Postoperative	7.2 (5.8-8.1)	6.6 (6.2-7.8)	7.4 (5.0-8.8)	1.00
pH				
- Preoperative	7.28 (7.22-7.35)	7.24 (7.1-7.33)	7.3(7.23-7.36)	.27
- During surgery	7.32 (7.25-7.38)	7.36 (7.28-7.49)	7.3(7.25-7.37)	.31
- Postoperative	7.22 (7.14-7.35)	7.22 (7.18-7.26)	7.21(7.1-7.35)	.86
Hemoglobin (mmol/L)				
- Preoperative	7.8 (7.2-8.7)	7.9 (7.2-8.2)	7.7 (7.1-8.9)	.90
- During surgery	7.8 (6.8-8.0)	7.3 (3.9-8.0)	7.8 (7.1-8.1)	.38
- Postoperative	7.8 (6.9-8.9)	7.4 (6.5-7.8)	8.6 (7.2-9.4)	.09
Lactate (mmol/L), median (range)				
- Preoperative	2.3 (1.1-10.6)	4.9 (1.1-10.6)	1.9 (1.3-4.6)	.45
- During surgery	2.7 (1.0-10.8)	2.0 (1.0-10.8)	3.0 (1.8-4.0)	.33
- Postoperative	2.3 (.9-10.9)	2.5 (0.9-10.9)	2.0 (1.4-3.4)	.95

Table 1. Continued

	Study group N = 19	CAR+ during surgery n = 7	CAR- during surgery n = 12	P value CAR+ vs. CAR-
Thrombocytes (*10^9/L), median (range)				
- Preoperative	106 (18-385)	99 (18-263)	150 (30-385)	.52
- Postoperative	74 (28-254)	69 (28-135)	76 (32-254)	.64
C-reactive protein (mg/L), median (range)				
- Preoperative	91 (1-283)	89 (25-283)	96 (1-149)	.76
- Postoperative	88 (1-203)	71 (52-71)	111 (1-203)	.63
Red blood cell transfusion during surgery (mL/kg)	19 (7-34)	20 (0-47)	19 (10-29)	1.00
Hemodynamically significant PDA	10 (53%)	1 (14%)	8 (67%)	.06
New cerebral lesions on first ultrasound postoperatively				
- GMH				
Grade I-II	-	-	-	-
Grade III-IV	-	-	-	-
- TPE	1 (5%)	-	1 (8%)	-
- PVL	-	-	-	-

Abbreviations: CAR+, adequate cerebrovascular autoregulation; CAR-, absent cerebrovascular autoregulation; wks, weeks; SIP, spontaneous intestinal perforation; GMH, germinal matrix hemorrhage; IVH, intraventricular hemorrhage; TPE, transient periventricular echodensities; PVL, periventricular leukomalacia. Data are expressed as median (IQR) or as numbers (percentage) unless otherwise specified; * $P < .05$.

Anesthesia

The total time spent in the operation room was median (IQR) 155 minutes (100-195). The median (IQR) end tidal sevoflurane concentration was 1.1% (0.7%-1.4%). The median (IQR) rocuronium and fentanyl doses were 1.4 (1.1-2.2) mg/kg, and 11.4 (7.2-13.8) µg/kg, respectively.

Cerebral oxygenation

Preoperatively, we found median (IQR) r_cSO_2 values of 64% (53-75), 65% (53-73) during surgery, and 72% (60-82) postoperatively. The cFTOE values were: preoperative, median (IQR) 0.30 (0.22-0.40), 0.30 (0.23-0.44) during surgery, and postoperative, 0.22 (0.16-0.36). The preoperative r_cSO_2 and cFTOE values did not differ from the r_cSO_2 (P = .14) and cFTOE (P = .39) values during surgery. We found higher r_cSO_2 and lower cFTOE values postoperatively compared to r_cSO_2 (P = .02) and cFTOE (P = .01) during surgery.

Mean arterial blood pressure

MABP was median (IQR) 35 (28-38) mm Hg preoperatively, 32 (30-36) mm Hg during surgery, and 35 (31-42) mm Hg postoperatively. We did not find any differences, using the Friedman test, in median MABP values comparing preoperative values, values during surgery, and postoperative values (P = .40).

Cerebral autoregulation

Preoperative combined MABP and cFTOE measurements were not taken in four out of the 19 preterm infants. In two infants postoperative combined MABP and cFTOE data were lacking. We found that three out of 15 infants (20%) had impaired CAR preoperatively, 12 out of 19 patients (63%) had impaired CAR during surgery, and none had impaired CAR postoperatively (Table 2). We found a higher incidence of impaired CAR during surgery compared to preoperatively (63% versus 19%, P = .01) and compared to postoperatively (63% versus none, P = .002). Of the 12 infants in whom we actually measured supposedly adequate CAR preoperatively, eight infants (67%) seemed to lose CAR during surgery (P = .01). Of these eight infants, none had impaired CAR postoperatively (P = .02)

Cerebral oxygenation and mean arterial blood pressure in infants with adequate and impaired CAR during surgery

Cerebral oxygen saturation values, cerebral FTOE values, and MABP values did not differ between infants with supposedly adequate CAR during surgery and infants who showed impaired CAR during surgery. Cerebral rSO_2 values were median (IQR) 70% (53-87) in infants with supposedly adequate CAR versus 64% (54-73) in infants with impaired CAR (P = .71). Cerebral FTOE values were median (IQR) 0.28 (0.13-0.45) in infants with supposedly adequate CAR versus 0.31 (0.24-0.43) in infants with impaired CAR, (P = .77). MABP values

during surgery were median (IQR) 33 (31-38) mm Hg in infants with supposedly adequate CAR versus 31 (29-36) mm Hg in infants with impaired CAR (*P* = .20). Seven (26%) infants showed a lower MABP during surgery in comparison to preoperative MABP measurements. Four of these infants seemed to lose CAR during surgery, whereas three infants did not.

Clinical and biochemical variables associated with impaired CAR

Two variables appeared significantly associated with impaired CAR during surgery in the univariate logistic regression models (Table 3).

First, a rise of 1kPa in PCO_2 resulted in a three times higher risk of absent CAR during surgery (OR 3.05, 95% CI, 1.11-8.12, *P* = .03). Median (IQR) PCO_2 values are depicted in Figure 2 for infants with CAR and impaired CAR during surgery. The PCO_2 values were lower during surgery compared to preoperative (3.7 kPa versus 5.8 kPa, *P* = .03), as well as postoperative values (3.7 kPa versus 6.6 kPa, *P* = .02), in infants who had supposedly adequate CAR during surgery. This was not the case for infants who had an impaired CAR during surgery (Figure 2). Furthermore, PCO_2 values were lower in the infants with supposedly adequate CAR in comparison to infants with impaired CAR during surgery (3.7 kPa versus. 6.0 kPa, *P* = .007).

Second, a rise of 0.1% in the end tidal volume of sevoflurane had a 1.42 greater risk of impaired CAR during surgery (OR 1.42, 95% CI, 1.01-1.99, *P* = .045). We found no associations between impaired CAR during surgery and GA, BW (z scores), the need for inotropics during surgery, the volume of RBC transfusion (mL/kg), or Hb values (Table 3).

Next, we constructed a multivariate model with the PCO_2, end tidal volumes of sevoflurane and GA. We found that only PCO_2 remained significantly correlated with CAR in the model (OR 3.05, 95% CI, 1.11-8.12, *P* = .03).

Table 2. Individual patient characteristics and Spearman rank correlations between MAPB and cFTOE

Infant	BW (g)	GA (wks + d)	NECSIP	Pre laparotomy			During laparotomy			Post laparotomy			Cranial ultrasound [1]
				MABP	cFTOE	Spearman's rho	MABP	cFTOE	Spearman's rho	MABP	cFTOE	Spearman's rho	
1	1750	31+2	SIP	59	0.22	-0.37*	36	0.25	-0.79**	48	0.18	-0.29**	-
2	1200	28+0	NEC	34	0.17	0.09*	36	0.17	-0.71**	34	0.06	-0.20**	-
3†	990	26+4	SIP	38	0.40	0.14**	38	0.46	-0.59**	-	0.36	-	-
4	975	26+1	SIP	33	0.29	0.003	30	0.23	-0.57**	35	0.23	0.26**	-
5	1000	26+6	SIP	27	0.30	-0.15**	32	0.19	-0.53**	35	0.21	0.14**	-
6	1650	36+3	NEC	-	0.26	-	43	0.25	-0.45**	38	0.17	-0.28**	-
7†	790	26+0	NEC	29	0.53	0.48	29	0.49	-0.45**	27	0.44	0.43*	TPE ↑
8	924	27+4	NEC	28	0.38	0.29*	23	0.44	-0.42*	31	0.35	0.48**	-
9†	815	25+6	NEC	26	0.34	-0.33**	29	0.32	-0.36**	-	-	-	-
10†	600	26+4	NEC	38	0.41	-0.23**	31	0.39	-0.33**	28	0.39	-0.03*	-
11†	1090	26+6	NEC	35	0.25	0.44**	35	0.32	-0.31**	33	0.32	-0.07*	-
12	810	26+5	NEC	26	0.32	-0.56**	30	0.30	-0.30**	37	0.21	0.12**	-
13	1100	26+6	NEC	-	0.51	-	31	0.47	-0.28	27	0.36	-0.28**	-
14	1100	28+6	NEC	36	0.20	0.23**	32	0.07	-0.22**	40	0.04	0.34**	-
15	1250	34+2	NEC	35	0.22	0.37**	33	0.13	-0.18**	35	0.12	0.46**	-
16†	1430	31+0	NEC	-	0.51	-	38	0.25	-0.12	41	0.19	0.20**	-
17	2636	36+1	NEC	52	0.26	0.63	36	0.28	0.09	42	0.09	0.54**	-
18	960	29+5	SIP	-	-	-	31	0.37	0.19**	54	0.48	-0.18**	-
19	1525	29+2	NEC	43	0.15	-0.03*	45	0.45	0.20	42	0.27	0.43**	-

Abbreviations: BW, birth weight; wks, weeks; d, days; SIP, spontaneous intestinal perforation; MABP, mean arterial blood pressure; cFTOE, cerebral fractional tissue oxygen extraction; ,TPE, transient periventricular echo densities, †, non- survivor; *, $P < .05$; **, $P < .01$. Impaired CAR : significant negative correlation coefficient between MABP and cFTOE of ≤0.3. [1] First cranial ultrasound post laparotomy: new pathology.

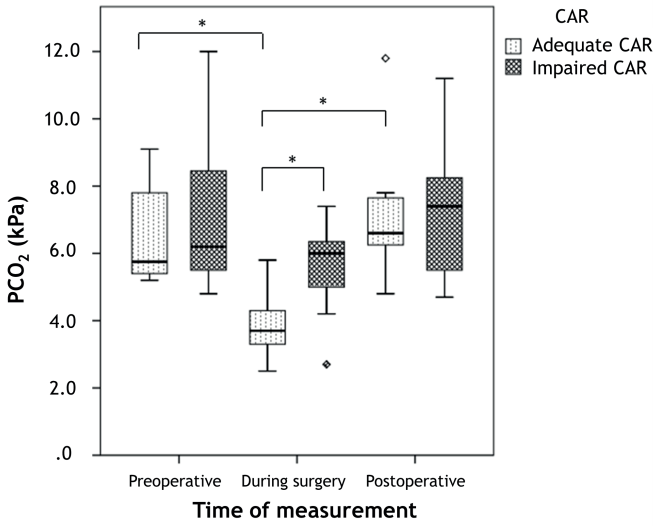

Figure 2. Perioperative PCO_2 values in preterm infants with supposedly adequate CAR and impaired CAR during laparotomy

The boxes represent the individual PCO_2 values between the 25th and 75th centiles (interquartile range); the whiskers represent the range of values, with the exception of outliers.Outliers are represented by the diamonds, defined as values between 1.5 interquartile range and 3.0 interquartile ranges from the end of a box. * *P* < .05 Abbreviations: CAR – Cerebrovascular autoregulation; pCO_2 – Partial carbon dioxide

Table 3. Univariate logistic regression analysis of clinical and biochemical data and their association with impaired CAR during laparotomy

Variable	CAR – (n = 12)	CAR + (n = 7)	OR	95% CI	*P* value
Gestational age (wks)	26.79 (26.25-27.89)	29.71 (28.86-34.29)	0.74	0.53-1.05	.09
Birth weight (z scores)	0.09 (-0.57-0.32)	-0.52 (-1.47-0.61)	1.45	0.46-4.53	.53
Treatment with inotropics during laparotomy (Yes/No)	4/3	7/5	1.05	0.16-6.92	.96
Partial carbon dioxide (kPa) during laparotomy	6.0 (4.9-6.5)	3.7 (2.9-4.7)	3.05	1.11-8.12	.03*
Hemoglobin (mmol/L) during laparotomy	7.8 (7.1-8.1)	7.3 (3.9-8.0)	2.01	0.76-5.28	.16
Red blood cell transfusion (mL/kg) during laparotomy	18.6 (10.4-29.1)	20.0 (0.0-46.6)	0.99	0.94-1.05	.73
Sevoflurane (end-tidal volume, 0.1%)	1.3 (1.0-1.6)	0.7 (.6-1.0)	1.42	1.01-1.99	.045*

Abbreviations: CAR, cerebrovascular autoregulation; CAR- ,absent cerebrovascular autoregulation; CAR+, adequate cerebrovascular autoregulation; wks, weeks. Data are expressed as median (IQR) or as numbers, unless otherwise specified; * stands for *P* < .05.

Preoperative and postoperative cerebral ultrasound examinations

Of the 17 infants that survived to have a postoperative cranial ultrasound, one infant showed increased transient periventricular echo densities in comparison to the last cerebral ultrasound preoperatively. These results are summarized in Tables 1 and 2.

DISCUSSION

The aim of this study was to evaluate evidence for the presence of impaired CAR, defined as a significant negative correlation between cFTOE and MABP, during laparotomy in preterm infants. We found that two thirds (67%) of the preterm infants in this study that showed evidence of CAR prior to surgery, seemed to lose CAR during laparotomy, and supposedly regained CAR after. Furthermore, we showed that a rise of 1kPa in PCO_2, obtained when clinically indicated, is associated with a three times greater risk of impaired CAR during surgery.

Although previous research demonstrated that infants who had undergone neonatal surgery experience neurodevelopmental delay later in life, to date the etiology has not been extensively investigated. Impaired CAR may lead to harmful fluctuations of cerebral perfusion. If this occurs during surgery, it might be one of these etiological factors that increases the risk of brain injury and of a poorer neurodevelopmental outcome in comparison to preterm infants who had not undergone major surgery.[6,7] Extremely preterm and critically ill preterm infants are less likely to regulate cerebral perfusion adequately.[9,12-14] This hold true for infants suffering from NEC as well.[26] Major surgery may represent an added risk of impaired CAR in these vulnerable infants. Our study showed that evidence for impaired CAR was displayed in more than half of the preterm infants during laparotomy.

Both hypercapnia, as well as hypocapnia is associated with harmful effects on the cerebral perfusion.[6,22,24,28] We found that for every 1.0 kPa increase in PCO_2, the risk of signs of impaired CAR increased approximately threefold. A higher PCO_2 has a vasodilatory effect on the smaller cerebral vessels, recently confirmed by Dix et al.[29] In preterm infants, using NIRS, they found that an acute increase in end tidal CO2 was associated with increased cerebral oxygenation.[29] Hypercapnia might reduce reactivity of the cerebral vessels and therefore increase the risk of impaired CAR.[28] The infants in our study with supposedly adequate CAR during surgery more often showed hypocapnia, with a median PCO_2 of 3.7 kPa during the laparotomy. We speculate that hypocapnia might be a result of mechanical hyperventilation. We did not record data on mechanical ventilation settings.

Little is known about the effect of vasodilatory anesthetic drugs, such as sevoflurane, on cerebral perfusion in preterm infants. It is suggested that sevoflurane might contribute to a pressure-passive cerebral circulation.[30] Although the dose of sevoflurane seemed to be associated with evidence of impaired CAR, this result did not persist in the multivariate model. This might be due to a mediation effect between the dose of sevoflurane and PCO_2,

or sevoflurane indeed hardly influences CAR, possibly due to low dosages. Finally, lack of power in this small sample may have led to underestimating the effect of sevoflurane.

A final possible explanation for evidence of impaired CAR during laparotomy addresses a low MABP during surgery.[31] It has been reported that MABP values below 30 mm Hg or above 60 mm Hgmight exceed the lower and upper thresholds to maintain supposedly adequate CAR.[32] The MABP values during surgery of infants included in our study were between 30 mm Hg and 60 mm Hg. Only three out of the 12 infants with impaired CAR during surgery showed a MABP below 30 mm Hg during surgery. Therefore a low MABP could not entirely explain our findings. Furthermore, the MABP was not lower or higher during surgery in comparison to preoperative and postoperative MABP measurements.

Although this was not the aim of our study, we demonstrated lower r_cSO_2 and higher cFTOE values prior to and during surgery in comparison to postoperative r_cSO_2 and cFTOE values. These results suggest that either cerebral perfusion increases or cerebral metabolism decreases postoperatively in preterm infants with NEC or SIP, because the regional tissue oxygen saturation depends on the balance between oxygen supply and consumption. Additionally, we found that the infants who survived the first eight hours after surgery showed evidence of adequate CAR. It remains unclear whether this increased cerebral oxygen saturation is related to an supposedly adequate CAR or that it may be a sign of recovery.

Cerebral ultrasound was performed before and after surgery. Although 67% of the infants seemed to lose CAR during surgery, we did not identify any new cerebral pathology on the ultrasound, performed one week after surgery, in 79% of these infants. It might be possible that cerebral lesions were present but not detected by cerebral ultrasound. A previous study by Stolwijk et al reported cerebral punctate white matter lesions detected with magnetic resonance imaging but not detected with cerebral ultrasound.[6] Furthermore, they observed parenchymal lesions in 75% of the preterm infants after surgery.

In addition to the small size of our sample lacking power to be able to assess all potential confounders, we acknowledge several other limitations of our study. The first limitation concerns the method to assess CAR. Using a statistically significant negative correlation between cFTOE and MABP over a longer period of time is a rather crude way of assessing CAR. It was suggested that CAR is a dynamic process, which fluctuates over time.[8] Unfortunately, our sampling frequency was too low to perform dynamic CAR assessments in more detail, using moving window correlation or transfer function.[10-18-21] Currently, the optimal method for assessing CAR is still under debate.[33] By calculating Spearman rank correlation coefficients over these longer periods of time, and setting the correlation coefficient threshold at ≤ -0.3,[21] we will have missed variations in CAR, and we may have both overestimated and underestimated impaired CAR.

Also, we were unable to assess the effect of all interventions on change in CAR in this small sample. Nevertheless, on the basis of our data we can hypothesize that the overall

incidence of impaired CAR is increased in preterm infants undergoing laparotomy, and we believe that this hypothesis is sufficiently plausible to warrant further research focusing on variations in CAR and the clinical variables affecting it, in larger populations..

Another limitation of our study addresses the use of near-infrared spectroscopy to assess cerebral perfusion. Currently, NIRS lacks high precision and shows high individual differences.[34,35] Nevertheless, it is a reliable method if it is used as a trend monitor to detect changes in oxygenation within one infant, which we then correlated with MAPB changes to address the presence of CAR. One also needs to keep in mind the fact that cFTOE is not only influenced by perfusion, but also relates to cerebral oxygen demand and consumption. Finally, we point out that we used the PCO_2 values collected from blood gases, which is a single measurement obtained if clinically indicated, instead of continuous end-tidal CO_2 measurements. End-tidal CO_2 measurements, however, are not always reliable during laparotomy in preterm infants.[36]

We conclude that more than half of the preterm infants with NEC or SIP display evidence of impaired CAR during laparotomy, whereas preoperatively and postoperatively they did seem to have adequate CAR. This might pose an extra risk of brain injury. Secondly, we showed that potentially impaired CAR during surgery might be associated with higher PCO_2 values. The exact mechanisms responsible for the supposed impaired CAR in preterm infants during surgery, and the relationship between impaired CAR and brain injury, requires further investigation so as to improve the neurodevelopmental outcomes of this group of infants in the future.

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